News and Views from the Literature

Benign Prostatic Hyperplasia

The Use of Botulinum Toxin in Men with Benign Prostatic Hyperplasia

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The use of botulinum toxin A (Botox®; Allergan, Inc., Irvine, CA) in the genitourinary tract has generated excitement over the past few years. Its use in patients with voiding dysfunction has been well described.[1] Because of the beneficial effect of botulinum toxin A on voiding symptoms, clinical trials to determine efficacy in patients with overactive bladder are now underway. It is not surprising that use of this agent in the prostate to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) is an emerging area of interest. This interest is due, in part, to enthusiasm for developing alternative therapies for BPH, particularly ones that can be done in an office setting. With the increased use of botulinum toxin in other parts of the body and, in particular, the urinary bladder, use of this agent in the prostate would seem to be a reasonable area to investigate.

Rationale for Use in the Prostate

Botulinum toxin A has been used to treat various types of skeletal muscle spasticity. Its mechanism of action is inhibition of acetylcholine release at the neuromuscular junction.[2] Why would it be effective in the prostate?

The prostate is innervated by sympathetic and parasympathetic efferents, as well as sensory afferents. Secretion is mediated by postganglionic cholinergic sympathetics, while postganglionic noradrenergic sympathetics mediate contraction in the prostate. Parasympathetic cholinergics may interact with the sympathetic nerves and influence both secretion and contraction.[3] The physiologic responses to neural stimulation in the prostate closely resemble those of sweat and salivary glands and the coordination of contraction and secretion during seminal emission and ejaculation are similar to that occurring in the pancreas during digestion.

The secretory role of cholinergic nerves is mediated by muscarinic receptors located on prostatic acini. Cholinergic nerves and muscarinic receptors are also located in the prostatic fibromuscular stroma, and around ducts and blood vessels. There is evidence that muscarinic receptor activation plays a role in cell growth of the normal and BPH prostate, including influencing the expression of growth factors, inducing cell transformation, and stimulating cell proliferation in normal, BPH, or prostatic cancer cells.[4-6] Therefore, inhibition of acetylcholine by botulinum toxin A in BPH patients may disrupt the neural control of the prostate and alterations in pelvic neuropeptides bringing symptomatic relief.[7]

Injection therapy for BPH has a history of more than a century. The initial injected materials treated prostatic obstruction through acute inflammation followed by

scarring and shrinkage of the prostate. Although multiple materials and methods of injection of the prostate have been proposed over time, few well designed studies exist.[8]

Innovations in minimally invasive therapy for BPH have become increasingly important in the past decade, as many patients, especially those who are young or who have multiple comorbidities, try to avoid surgery because of peri- and postoperative risks. Interest in the investigation of prostatic injection has increased in the face of increasing numbers of older patients who are poor surgical candidates and fail medical therapy.

Botulinum toxin A has evolved recently from a deadly poison to a pharmaceutical agent with great potential. Botulinum toxin A functions through blockade of the release of neurotransmitters at the synaptic cleft. The most obvious result is flaccid paralysis secondary to blockage of acetylcholine release. However, the release of other transmitters including, but not limited to, noradrenaline, dopamine, and serotonin is also impeded.[9]

Current US Food and Drug Administration-approved indications for botulinum toxin A injection therapy are limited to glabellar frown lines, axillary hyperhydrosis, cervical dystonia, blepharospasm, and strabismus.[10] Recently, injection of botulinum toxin A into the prostate for treatment of severe, medically refractory BPH has been investigated.

The first studies were conducted by Doggweiler and associates[7] in murine prostates in 1998. The rationale for this investigation was that the prostate is an end organ and that its function is rooted in its neural regulation. Thus, by altering the neural control, the prostate itself will be altered. The investigators were especially intrigued by the unique aspect of the absence of necrosis or inflammation in tissues affected by botulinum toxin A. The final pathology and histology in the murine prostates revealed decreased prostatic weight with repeat injection, as well as a generalized atrophy of the glands. Three papers published more recently reported results of human trials.

Relief by Botulinum Toxin of Voiding Dysfunction Due to Benign Prostatic Hyperplasia: Results of a Randomized, Placebo-Controlled Study

Maria G, Brisinda G, Civello IM, et al.

Urology. 2003;62:259-264.

Botulinum Toxin A Improves Refractory Benign Prostatic Hyperplasia Symptoms

Chuang YC, Chiang PH, Huang CC, et al.

J Urol. 2004;171(suppl):201 [abstract].

Prostate Botulinum A Toxin Injection—An Alternative Treatment for Benign Prostatic Obstruction in Poor Surgical Candidates

Kuo H.

Urology. 2005;65:670-674.

The first reported human prostatic injection of botulinum toxin A was in 2003. In that study, Maria and colleagues injected 200 U of botulinum toxin A into the prostate through a perineal approach using ultrasound guidance. Although the study followed only a small cohort of patients for 2 month after injection, the initial results were impressive. Those who received botulinum toxin A had significant improvement in their American Urological Association (AUA) symptom scores when compared to those receiving placebo. The treatment group also had decreased prostate-specific antigen (PSA) levels and postvoid residual volume (PVR) and increased peak urinary flow when compared to the placebo group. Of great interest was their observation that there was a 50% reduction in prostate volume at 1 month and a total reduction of 33% from baseline volume at 2 months. No side effects were reported by any patient receiving botulinum toxin A.

Chuang and associates used half the dosage of botulinum toxin A (100 U) in their study, and also found significant improvement in AUA symptom score as well as in peak urinary flow. However, there was little to no decrease in the volume of the prostate.

The only reported study using transurethral botulinum toxin A injection used 200 U diluted and divided for 10 injection sites. No placebo group was included in this study. All patients were evaluated pre- and posttreatment with video urodynamics, which demonstrated a significant decrease in both voiding pressure and PVR. Significant improvement in urine flow rate and decreased prostate volume were also evident. Most impressively, the maximal effects appeared 1 week after treatment. These patients were followed up for up to 1 year with continued good results and overall improved quality of life without the need for repeat injections.

At the recent AUA annual meeting, a number of abstracts were presented on the use of botulinum toxin A in men with BPH. In 16 men with larger prostate volumes ($>$ 80 mL) who were injected with 150 U of botulinum toxin A into each lobe of the prostate, there was significant improvement in peak flow rate (Q_{max}) from 8.2 to 18.1 mL/s and a reduction in prostate weight from 106 to 53 g at 6 months.[11] In another study, 40 men were treated with either 50 or 100 U of botulinum toxin A to each lobe in a 2:1 treated-to-sham, double-blind study. There was improvement in both symptoms (International Prostate

Symptom Score decrease from 21.2 to 11.4) and Q_{max} (10.4 to 13.9) with only 1 patient going into urinary retention.[12]

Although the preliminary studies available are encouraging, many questions are still to be answered. The exact mechanism by which botulinum toxin A reduces prostate volume and decreases urethral resistance is still unclear. Not enough information is available to predict the response of the prostate over longer periods of time. Will the tissue regenerate? If so, how long will the effects of botulinum toxin A last? Along with the decrease in prostate volume, serum PSA decreases. It remains to be seen how this effect of botulinum toxin A affects the ability of PSA to be used as a screening tool for prostate cancer. Moreover, we do not know how the involution of the tissue will affect the histopathology of the prostate when being evaluated for cancer.

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Another important aspect not addressed is the possibility of sexual side effects. Transurethral resection of the prostate as well as medical therapy with some agents can result in ejaculatory dysfunction. If botulinum toxin A blocks the neuromuscular junction it seems plausible that patients could have ejaculatory changes after injection.

Finally, the issue of whether injection of the prostate with botulinum toxin A is cost effective will need to be examined. Durability of response will be the hallmark of assessing economic viability of this emerging therapy. Based on the 3 studies that are available, 200 U appears to have a better efficacy than 100 U in the treatment of BPH. Although it requires an outpatient procedure with minimal sedation and post-operative care, botulinum toxin A significantly increases the cost of the procedure.

In summary, injection of the prostate with botulinum toxin A is currently a promising prospective therapy. Many questions on long-term results and histological effects of injection have yet to be answered. Further prospective, blinded, placebo-controlled studies with long-term follow-up are needed to fully evaluate this novel application of botulinum toxin A. ■

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Prostate Cancer

Detecting Prostate Cancer with Molecular Markers: uPM3

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Prostate cancer is a major public health burden. In 2005, more than 232,000 new cases and 30,000 deaths from the disease are expected.[1] One of the main ways in which we screen for prostate cancer is through the use of serum prostate-specific antigen (PSA). Recently, however, the value of PSA as a screening tool has been questioned because it has become increasingly clear that many men with a "normal" PSA level can nevertheless have prostate cancer.[2] New diagnostic measures are clearly needed. One approach, which is now commercially available, is the uPM3™ urine test (DiagnoCure; Quebec City, Quebec, Canada). This test is the first molecular test for prostate cancer screening. The uPM3 relies on the fact that prostate cancers have increased expression of a noncoding ribonucleic acid (RNA), differential display code 3 (DD3).[3] The function of DD3 remains elusive; however, the fact that it is expressed at high levels by prostate cancers and at only